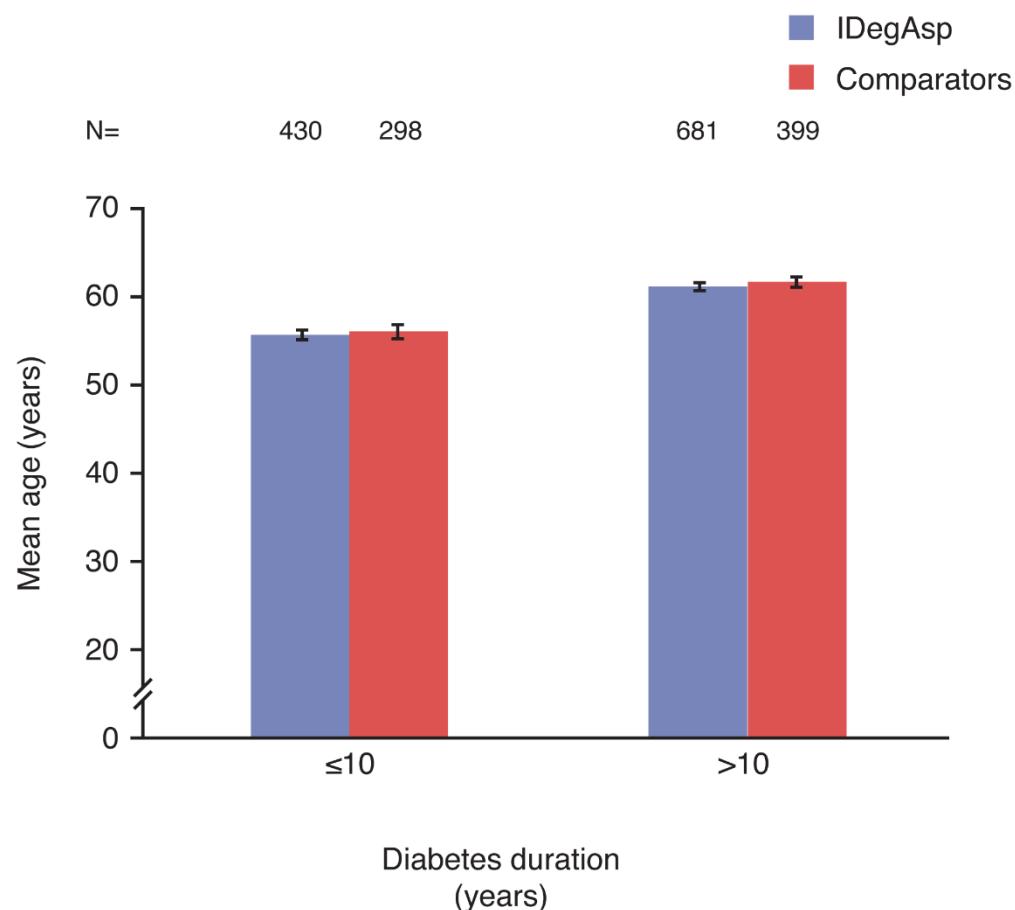


Supplementary Material:

The coformulation of insulin degludec and insulin aspart lowers fasting plasma glucose and rates of confirmed and nocturnal hypoglycaemia, independent of baseline glycated haemoglobin levels, disease duration or body mass index: A pooled metaanalysis of phase III studies in patients with type 2 diabetes

Figure S1. Mean age by disease duration (years)

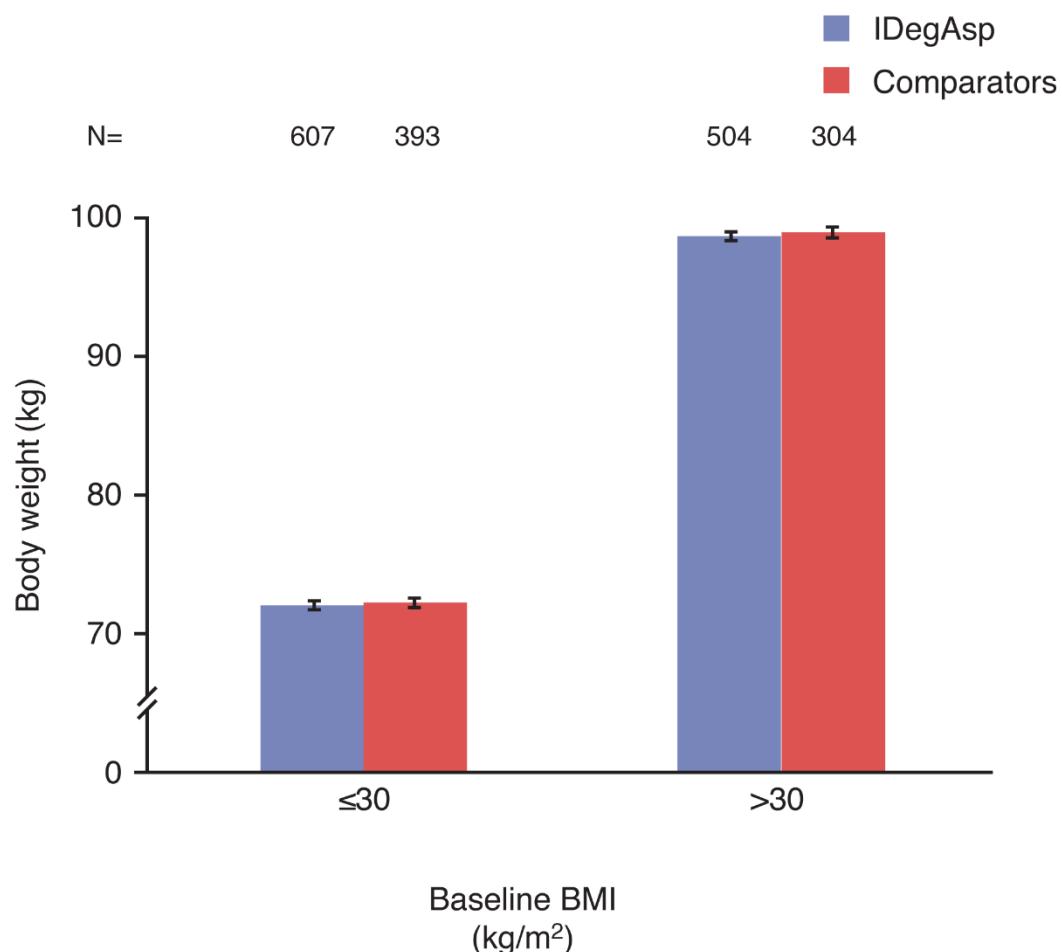


Diabetes duration
(years)

Data are mean (SEM) from FAS, LOCF. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530). Trial NCT01680341: IDegAsp Simple and IDegAsp step-wise arms are considered within the IDegAsp group.

BIAsp 30, biphasic insulin aspart 30; FAS, full analysis set; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; LOCF, last observation carried forward; OD, once daily.

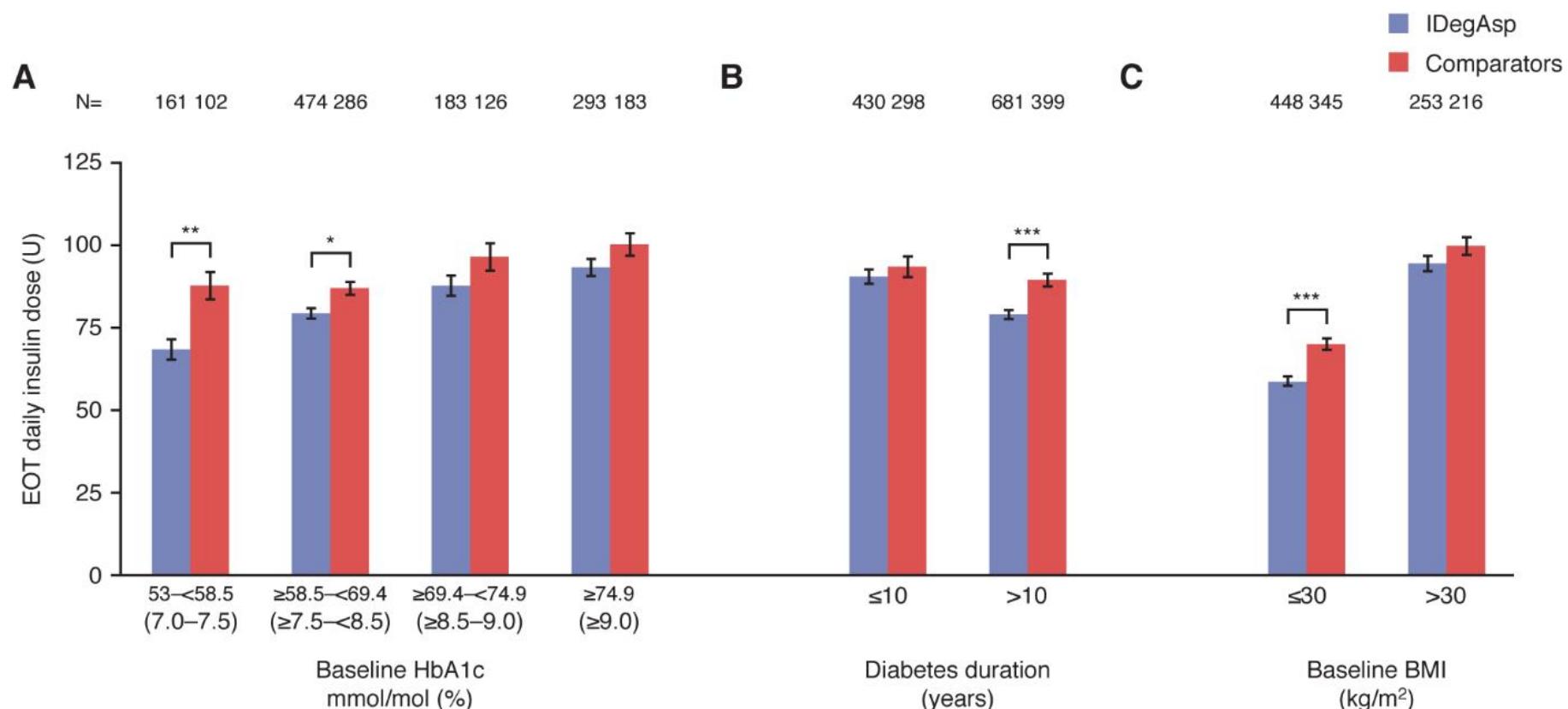
Figure S2. Body weight (kg) EOT by baseline BMI (kg/m^2)



Data are mean (SEM) from FAS, LOCF. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530); Trial NCT01680341: IDegAsp Simple and IDegAsp step-wise arms are considered within the IDegAsp group.

BIAsp 30, biphasic insulin aspart 30; FAS, full analysis set; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; LOCF, last observation carried forward; OD, once daily. Trials used for statistical analysis comprised NCT01009580, NCT01059812, NCT01513590, NCT01680341 and NCT01713530.

Figure S3. Total daily insulin dose (U) at EOT, stratified by: **a**) HbA1c categories (%); **b**) diabetes duration (years); and **c**) BMI (kg/m^2)



Data are mean (SEM) from FAS, LOCF. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530); Trial NCT01680341: IDegAsp Simple and IDegAsp step-wise arms are considered within the IDegAsp group.

BIAsp 30, biphasic insulin aspart 30; EOT, end of trial; FAS, full analysis set; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; LOCF, last observation carried forward; OD, once daily. Trials used for statistical analysis comprised NCT01009580, NCT01059812, NCT01513590, NCT01680341 and NCT01713530.

Table S1. Baseline characteristics.

	START TWICE DAILY ² NCT01513590		INTENSIFY PREMIX I ⁴ NCT01009580		INTENSIFY ALL ³ NCT01059812		SIMPLE vs. STEP-WISE BID ⁵ NCT01680341 ^a		TWICE DAILY vs. BASAL-BOLUS ¹ NCT01713530 ^b	
Patient characteristic	Insulin-naïve treated with metformin ±1 OAD for ≥3 months		Previously treated with basal–bolus, premixed or self-mixed insulin ± OADs for ≥3 months		Asian patients previously treated with basal, premixed or self-mixed insulin ± metformin for ≥3 months		Currently treated with stable doses of IGlar U100 + ≤3 OADs for ≥3 months		Currently treated with basal insulin ± OADs for ≥3 months	
Treatment arm	IDegAsp BID	BIAsp 30 BID	IDegAsp BID	BIAsp 30 BID	IDegAsp BID	BIAsp 30 BID	IDegAsp Step-wise BID	IDegAsp Simple BID	IDegAsp BID	IDeg OD + IAsp
Full analysis set (n)	197	197	224	222	280	142	136	136	138	136
Female/male (%)	48.2/51.8	48.7/51.3	42.4/57.6	46.4/53.6	46.1/53.9	44.4/55.6	39.0/61.0	44.1/55.9	47.1/52.9	36.8/63.2
Age (years)	59.0 (±9.5)	58.8 (±8.4)	58.7 (±9.9)	58.8 (±9.8)	59.1 (±10.2)	61.2 (±9.5)	59.1 (±9.4)	58.8 (±9.8)	59.6 (±8.3)	59.6 (±9.2)
Weight (kg)	88.0 (±15.0)	88.5 (±14.9)	81.5 (±18.1)	78.9 (±17.6)	66.1 (±11.2)	66.0 (±11.2)	89.4 (±17.4)	89.4 (±19.3)	91.2 (±17.7)	93.3 (±15.2)
BMI (kg/m ²)	31.2 (±4.3)	31.1 (±4.2)	29.6 (±4.6)	29.0 (±4.9)	25.4 (±3.4)	25.4 (±3.7)	31.5 (±4.7)	31.7 (±4.8)	32.3 (±4.7)	32.0 (±4.5)
Duration of diabetes (years)	9.6 (±6.1)	9.4 (±5.7)	12.8 (±6.8)	13.1 (±7.4)	16.3 (±7.9)	16.3 (±8.2)	11.2 (±6.7)	13.0 (±7.0)	13.5 (±7.2)	11.7 (±7.2)
HbA1c (%)	8.5 (±0.8)	8.3 (±0.7)	8.3 (±0.8)	8.4 (±0.9)	8.4 (±0.8)	8.4 (±0.9)	8.2 (±0.9)	8.2 (±0.9)	8.3 (±0.9)	8.3 (±0.7)
HbA1c (mmol/mol ^c)	69.0 (±8.7)	67.0 (±7.7)	67.2 (±8.7)	68.3 (±9.8)	68.3 (±8.7)	68.3 (±9.8)	66.6 (±9.4)	66.3 (±9.8)	67.2 (±9.8)	67.2 (±7.7)
FPG (mmol/l)	10.5 (±2.4)	10.0 (±2.3)	8.9 (±2.9)	8.6 (±2.6)	7.9 (±2.5)	7.9 (±2.5)	8.1 (±3.0)	7.8 (±2.3)	9.0 (±3.0)	8.8 (±2.9)

Values are mean (SD) unless stated. ^aIn this trial, two different titration regimens were compared: simple titration (following a single pre-breakfast and pre-dinner SMPG measurement) involving twice-weekly up- or down-titration by 2 U; and step-wise titration (based on the lowest of three pre-breakfast and three pre-evening meal SMPG values) involving once-weekly up- or down-titration of 2–8 and 2–4 U, respectively. ^bIn this trial, the comparator arm was basal–bolus therapy. ^cCalculated not measured. BIAsp 30, biphasic insulin aspart 30; BID, twice daily; BMI, body mass index; FPG, fasting plasma glucose; IAsp, Insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IGlar U100, insulin glargine U100; OAD, oral antidiabetic drug; OD, once daily; SMPG, self-monitored plasma glucose.

Table S2. Summary of efficacy data

Endpoint	EOT HbA1c(%)				EOT HbA1c(mmol/mol ^a)				EOT FPG (mmol/l)				
Treatment	N (IDegAsp/ Comparato rs)	IDegAsp (SEM)	Comparators (SEM)	Significance (<i>p</i> < 0.05)	N (IDegAsp/ Comparators)	IDegAsp (SEM)	Comparators (SEM)	Significance (<i>p</i> < 0.05)	N (IDegAsp/ Comparators)	IDegAsp (SEM)	Comparators (SEM)	Significance (<i>p</i> < 0.05)	
HbA1c categories (mmol/mol)													
	53.0-<58.5	161/102	6.48 (± 0.05)	6.45 (± 0.07)	NS	161/102	47.29 (± 0.55)	47.01 (± 0.71)	NS	-	-	-	
	$\geq 58.5\text{--}<69.4$	474/286	6.76 (± 0.03)	6.72 (± 0.05)	NS	474/286	50.36 (± 0.37)	49.91 (± 0.49)	NS	-	-	-	
	$\geq 69.4\text{--}<74.9$	183/126	7.08 (± 0.06)	6.97 (± 0.08)	NS	183/126	53.87 (± 0.70)	52.67 (± 0.85)	NS	-	-	-	
	≥ 74.9	293/183	7.33 (± 0.06)	7.33 (± 0.08)	NS	293/183	56.65 (± 0.67)	56.64 (± 0.87)	NS	-	-	-	
Duration of diabetes (years)													
Baseline grouping	≤ 10	430/298	6.87 (± 0.05)	6.94 (± 0.06)	NS	430/298	51.63 (± 0.49)	52.35 (± 0.60)	NS	428/293	6.12 (± 0.12)	6.94 (± 0.14)	***
	>10	681/399	6.95 (± 0.03)	6.85 (± 0.04)	NS	681/399	52.44 (± 0.33)	51.36 (± 0.43)	NS	681/399	5.81 (± 0.08)	6.86 (± 0.11)	***
BMI (kg/m²)													
	≤ 30	607/393	6.98 (± 0.03)	6.99 (± 0.04)	NS	607/393	52.82 (± 0.37)	52.93 (± 0.47)	NS	607/393	5.76 (± 0.09)	6.79 (± 0.11)	***
	>30	504/304	6.84 (± 0.04)	6.77 (± 0.05)	NS	504/304	51.21 (± 0.42)	50.45 (± 0.55)	NS	504/304	6.14 (± 0.11)	7.00 (± 0.14)	***
FPG (mmol/L)													
	<5.5	-	-	-	-	-	-	-	115/55	5.50 (± 0.19)	6.06 (± 0.28)	NS	
	$\geq 5.5\text{--}<7.0$	-	-	-	-	-	-	-	206/112	5.40 (± 0.13)	6.28 (± 0.19)	**	
	$\geq 7.0\text{--}<10.0$	-	-	-	-	-	-	-	463/324	5.72 (± 0.09)	6.72 (± 0.11)	***	
	≥ 10.0	-	-	-	-	-	-	-	323/200	6.74 (± 0.16)	7.70 (± 0.20)	**	

Data are mean (SEM) FAS; LOCF. ** $p < 0.001$; *** $p < 0.0001$. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530); Trial NCT01680341: IDegAsp Simple and IDegAsp Step-wise arms are considered within the IDegAsp group. ^aCalculated not measured. BIAsp 30, biphasic insulin aspart 30; EOT, end of trial; FAS, full analysis set; FPG, fasting plasma glucose; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; LOCF, last observation carried forward; OD, once daily. Trials used for statistical analysis comprised NCT01009580, NCT01059812, NCT01513590, NCT01680341 and NCT01713530.

Table S3. Summary of hypoglycaemia data

Endpoint		Confirmed hypoglycaemia, events per 100 PYE				Nocturnal confirmed hypoglycaemia, events per 100 PYE			
Treatment		N (IDegAsp/ Comparators)	IDegAsp	Comparators	Rate ratio (CI)	N (IDegAsp/ Comparators)	IDegAsp	Comparators	Rate ratio (CI)
Baseline grouping	HbA1c categories (%)								
	7.0–7.5	161/102	797.94	1201.25	0.66* (0.459; 0.961)	161/102	73.45	136.50	0.54* (0.330; 0.879)
	≥7.5–<8.5	474/286	791.61	1092.94	0.72** (0.578; 0.907)	474/286	86.05	198.01	0.43*** (0.301; 0.628)
	≥8.5–<9.0	183/126	675.78	997.93	0.68* (0.491; 0.933)	183/126	67.86	165.87	0.41** (0.234; 0.715)
	≥9.0	293/183	869.59	1174.74	0.74* (0.550; 0.997)	293/183	81.97	225.72	0.36*** (0.224; 0.588)
	Duration of diabetes (years)								
	≤10	430/298	623.87	1023.54	0.61** (0.471; 0.788)	430/298	60.96	193.91	0.31*** (0.203; 0.487)
	>10	681/399	907.63	1200.92	0.76** (0.637; 0.896)	681/399	97.26	204.28	0.48*** (0.363; 0.624)
	BMI (kg/m ²)								
	≤30	607/393	949.25	1171.71	0.81* (0.671; 0.978)	607/393	95.15	219.79	0.43*** (0.314; 0.598)
	>30	504/304	592.66	1077.9	0.55*** (0.445; 0.680)	504/304	69.44	181.81	0.38*** (0.273; 0.534)

Data are mean (SEM) FAS; LOCF. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530); Trial NCT01680341: IDegAsp Simple and IDegAsp Step-wise arms are considered within the IDegAsp group.

BIAsp 30, biphasic insulin aspart 30; EOT, end of trial; FAS, full analysis set; FPG, fasting plasma glucose; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; LOCF, last observation carried forward; OD, once daily; PYE, patient-year of exposure. Trials used for statistical analysis comprised NCT01009580, NCT01059812, NCT01513590, NCT01680341 and NCT01713530. Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded plasma glucose <3.1 mmol/L (56 mg/dL). Nocturnal period: the period between 00:01 and 05:59 am (both inclusive). Severe hypoglycaemia: subject unable to treat himself/herself.

Table S4. Summary of insulin dose data

Total daily insulin dose (U)*	N (IDegAsp/ Comparator)	IDegAsp (SEM)	Comparator (SEM)	Treatment difference (95% CI)
HbA1c categories (%)				
7.0–7.5	161/102	68.65 (3.16)	88.01 (4.07)	5.436 (-30.07; -8.65)**
≥7.5–<8.5	474/286	79.28 (1.84)	86.91 (2.41)	3.142 (-13.80; -1.47)*
≥8.5–<9.0	183/126	87.87 (3.37)	96.70 (4.09)	5.490 (-19.63; 1.98) NS
≥9.0	293/183	93.39 (2.79)	100.24 (3.57)	4.679 (-16.05; 2.34) NS
Duration of diabetes (years)				
≤10	430/298	90.61 (2.31)	93.96 (2.81)	3.802 (-10.81; 4.12) NS
>10	681/399	78.91 (1.53)	89.58 (2.02)	2.614 (-15.80; -5.54)***
BMI (kg/m²)				
≤30	448/345	58.95 (1.34)	70.30 (1.54)	2.062 (-15.40; -7.31)***
>30	253/216	94.58 (2.42)	99.87 (2.60)	3.574 (-12.31; 1.74) NS

Data are from FAS. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$. Trials used for statistical analysis comprised NCT01009580, NCT01059812, NCT01513590, NCT01680341 and NCT01713530. Comparator: BIAsp 30 (NCT01009580, NCT01059812, NCT01513590), IDeg OD + IAsp (NCT01713530). Trial NCT01680341: IDegAsp Simple and IDegAsp Step-wise arms are considered within the IDegAsp group.

BIAsp 30, biphasic insulin aspart 30; EOT, end of trial; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; N, number of patients; OD, once daily.

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